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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,333	05/24/2005	Edith Dellacherie	122536	8802

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EXAMINER	
PALENIK, JEFFREY T	

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1615	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,333	DELLACHERIE ET AL.	
	Examiner	Art Unit	
	Jeffrey T. Palenik	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *8,19 and 21-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-18 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *25 Jan 2005 and 5 April 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

The Examiner thanks the Applicants for their timely reply filed on 12 December 2007, in the matter of 10/522,333.

Applicants' election **with traverse** of Group I, claims 1-20 is acknowledged. Applicants' election **with traverse** of saturated alkyl chains having a chain length ranging from 15-20 carbon atoms and nanoparticles is also acknowledged. Applicants traverse the election requirements on the grounds that the core particle taught by Lee et al. (USPN 5,753,234) is not based on an organosoluble polymer and thus "does not teach each and every element of 1".

Applicants' remarks have been fully considered and are found to be persuasive.

However, after further consideration of the prior art, a new lack of unity follows wherein the inventions listed in Groups I and II still do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding technical feature(s) because Illum (USPN 4,904,479) teaches 60 nm polystyrene microparticles which are coated with a poloxamer compound (Example 3). Materials other than poloxamer compounds are taught as comprising the coating agent and include such polymers as those which are esterified to produce suitable hydrophobic domains as well as natural materials such as hyaluronic acid (col. 10, lines 34-41).

Applicants' provisional elections of Group I and the respective species, as discussed above, stand. Furthermore, claims 8, 19 and 21-24 remain provisionally withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention and species, there being no allowable generic or linking claim. Applicants timely traversed the

restriction (lack of unity) requirement between the particle composition and the distinct compositions comprising said particle composition.

The remaining claims 1-7, 9-18 and 20 are presented and represent all claims under consideration.

Information Disclosure Statement

Two information Disclosure Statements (IDS), filed 25 January 2005 and 5 April 2005, are acknowledged and have been reviewed.

Claim Objections

Claim 9 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants are required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. As presently recited, claim 9 recites a limitation to the biodegradable organosoluble polymer of claim 1 wherein it is derived from either a synthetic or natural biodegradable polymer. Since a given substance is created either naturally or by "hand-of-man" (e.g. synthetically), it is unclear how the option of the polymer's origin further limits claim 1. Herein, for the purposes of examination on the merits, the Examiner interprets claim 9 as reciting the same patentable subject matter as claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9-18 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "is based on" as recited in claim 1 renders the claim indefinite because it is unclear how the component of "at least one biodegradable organosoluble polymer" is structurally related to the core of the particle. Herein, and for the purposes of examination on the merits, the Examiner broadly and reasonably interprets the particle core of claim 1 as ***comprising*** at least one biodegradable organosoluble polymer.

The term "at least partially" in claim 1 is a relative term which renders the claim indefinite. The term "at least partially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The parameter or limitation in the claim which is rendered indefinite by use of the above term is degree to which the instantly claimed particle is surface-coated.

Claim 1 recites the limitation "the carboxylic functions" in line 4 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Regarding claim 3, the phrase "which may be" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Regarding claim 4, the phrase "in particular" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 5 recites the limitation "the alkyl chains" in line 2 of the claim. There is insufficient antecedent basis for this limitation in the claim. Herein, and for the purposes of examination on the merits, claim 5, in light of the rejection, is interpreted by the Examiner as reciting the same subject matter and limitations as claim 1.

The limitation of claim 12 which states that the particle further "comprises at least one biological or synthetic active substance encapsulated in the polymer core" renders the claim indefinite. It is not clear if the active substance which is further included is itself encapsulated within the core of the particle or if it is contained anywhere within an encapsulated particle as whole. Herein, and for the purposes of examination on the merits, the Examiner broadly and reasonably interprets the limitation as reciting the active substance is contained anywhere within the whole encapsulated particle.

Claim 15 recites "medicinal product type" in the preamble of the claim as a limitation to the synthetic active substance of the instantly claimed particle. Per MPEP §2173.05(b)(E), the term "type" renders the claim indefinite since it is unclear what the term "type" is intended to convey.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex*

parte Wu, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 17 recites the broad particle size range of 50 nm to 600 μm (equal to 600,000 nm), and the claim also recites a particle size range of 80-200,000 nm, which is the narrower statement of the range/limitation. Herein, and for the purposes of examination on the merits, the Examiner broadly and reasonably interprets the limitation to recite the particle size range of 50-600,000 nm.

The remaining claims are rejected as being dependent from the above rejected claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-7, 9-18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ottoboni et al. (WO 98/48783) in view of Dellacherie et al. (FR 2794763; machine translation) and Illum (USPN 4,904,479).

The instant claims are drawn to a micro- or nanoparticle wherein the core of the particle is comprised of at least one biodegradable organosoluble polymer and has an amount of at least one amphiphilic hyaluronan derivative on its surface (claims 1-7, 9, 18 and 20). Claims 2 and 20 each recite limitations which are directed to product-by-process limitations, which per MPEP §2113, hold no patentable weight. Claims 3-7 recite limitations to the hydrophobic group(s) attached to the hyaluronan derivative of claim 1, further limiting the composition in terms of number of carbon atoms, type of chain and degree of esterification. Claims 10 and 11 further limit the biodegradable organosoluble polymer component. The particle composition is recited as further encapsulating an active agent (claims 12-14). Claim 15 further limits the biological active substance to one which has been synthetically derived. The Examiner interprets the limitation "synthetic active substance" as broad and reasonably comprising a compound which has been "produced artificially" (see *Merriam-Webster Online Dictionary*). Claim 16 recites that the composition comprises up to 95% of an active substance and claim 17 further limits the size of the particle.

Ottoboni et al. teach a microparticle composition containing solid-core, microparticles having diameters within the range of about 1-10 microns (1,000-10,000 nm), an outer layer of a biologically compatible material and an inner layer comprising a biodegradable polymer (claims

1 and 4). The biological compatible coating (e.g. outer layer) is taught as being a biopolymer protein which may comprise materials such as glycosaminoglycan (claims 33, 34 and 36). Ottoboni further defines glycosaminoglycans as including hyaluronic acid and chondroitin sulfate (pg. 5, lines 18-19). Claims 38-41 teach the biodegradable polymer as comprising synthetic polymers of polycaprolactone, polylactide, polyglycolide, or copolymers of caprolactone, lactic or glycolic acids. Claim 9 teaches the microparticles as containing a drug, which is interpreted by the Examiner to inherently teach that the particles comprise an amount of drug greater than 0% and less than 100% by weight of the composition.

Ottoboni does not teach the instantly claimed hydrophobic modifications made to the glycosaminoglycan proteins of the outer layer of the particles. Despite teaching the inclusion of a drug within the coated microparticle composition, no specific type or category of drug is expressly taught. Similarly, there is no express teaching of an upper limit of active substance of 95% by weight of the composition.

Dellacherie et al. teach a composition containing a modified hyaluronan which consists mainly of hyaluronic acid (HA) in which a proportion of not more than 50% of carboxylic acid groups are modified with aliphatic esters side-chains, each of which include at least 10 carbon atoms (claim 1). It is taught that derivatives of the invention have a rate of esterification which is usually at least 1%, and more specifically taught that modified hyaluronans may be obtained where the rate of esterification is approximately 4% for an 18-carbon alkyl chain (pg. 2, lines 7-8 and 19-21). The invention is further directed to the above compositions wherein the aliphatic branches range in length from 10-22 carbon atoms (pg. 4, line 29 to pg. 5, line 3). The

composition is taught as containing living cells and/or growth factors (claim 8). Other active hydrophobic agents such as steroid hormones, antibiotics, and anesthetics, are also taught as being incorporated (e.g. encapsulated) into the microsphere compositions (pg. 8, line 22 to pg. 9, line 18). Claims 9 and 10 teach that the esterified carboxylic groups is high enough to prevent dissolution of the composition in an aqueous salt solution, yet low enough to such that the modified hyaluronan swells in water like a hydrogel. Claim 11 further limits the composition of claims 9 and/or 10 such that the composition may take more specific forms such as microparticles or nanoparticles. The microsphere and nanosphere particles are further taught as not exceeding an average diameter of especially 500 microns (pg. 7, lines 26-30).

Dellacherie does not expressly teach the particle composition as being comprised of the biodegradable organosoluble polymers as instantly claimed. There is also no express teaching of an upper limit of active substance of 95% by weight of the composition.

Illum teaches microparticles based on at least one biodegradable organosoluble polymer (e.g. polystyrene) further characterized that said particles are surface-coated with at least one material hyaluronic acid and polymers that are esterified to produce suitable hydrophobic domains (col. 10, lines 34-41). The hydrophobic domains which may be attached are taught as including hydrophobic moieties such as esterified maleic acid groups (col. 2, lines 31-34). Claims 1 and 5 teach the microparticles as containing a drug, which is interpreted by the Examiner again, to inherently teach that the particles comprise an amount of drug greater than 0% and less than 100% by weight of the composition. Drugs taught as being administered from the microparticles include macrophage activating agents, anti-leukemia agents and

immunosuppressants (col. 10, lines 10-22). Microparticle diameters are taught as being 60 nm (Example 3).

Illum does not expressly teach that the hydrophobic groups are specifically attached to the hyaluronan and thus the does not teach sizes of the alkyl chains attached or the degree to which esterification occurs. Hyaluronic acid is taught, however, not as an encapsulated active substance. Similarly, chondroitin sulfate and glucosamine are also not taught.

In view of the combined teachings of the prior art, one of ordinary skill in the pharmaceutical or biomedical art, at the time of the invention, would have been motivated to combine an outer coating comprising hydrophobically-modified (e.g. esterified) domains and hyaluronic acid as taught by Illum, and an esterified, hydrophobically-modified amphiphilic hyaluronan derivative as taught by Dellacherie et al. with a particle composition whose core is comprised of a biodegradable, organosoluble material and an active agent as taught by Ottoboni et al. Such would have been obvious in the absence of evidence to the contrary since it is further taught that the hyaluronic acid (e.g. glycosaminoglycan) outer layer surface of the microparticle composition, which is practiced by both Illum (col. 2, lines 31-34 and col. 10, lines 34-41) and Ottoboni et al. (pg. 5, lines 13-14 and pg. 9, lines 9-18), is capable of being chemically modified to adjust the hydrophilicity of the particle such that it could accommodate exposure to different environments such as blood (pg. 5, lines 13-14 and pg. 9, lines 9-18). Additionally, Dellacherie et al. and Illum teach that both hydrophilic and hydrophobic active substances, which may be incorporated into the microsphere composition thereby indicating that alterations to the degree of

esterification to the hyaluronan component of the practiced invention will similarly impact the degree of hydrophilicity.

A person of ordinary skill in the art would have a reasonable expectation of success in modifying a hyaluronan-based, glycosaminoglycan-coated microparticle composition of Ottoboni using the alkyl chain esterification taught by Dellacherie et al. since the combined teachings disclose the instantly claimed coated pharmaceutical particles.

None of the references expressly teach the upper limit of active substance of 95% by weight of the composition, as claimed by Applicants. Since the values and formats of each parameter with respect to the claimed composition are adjustable, it follows that each is a result-effective parameter that a person having ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. However, the claims (i.e. claims 1 and 5 of Illum, claim 9 of Ottoboni et al. and claim 8 of Dellacherie et al.) teach the presence of an active substance encapsulated within their respective compounds, thereby inherently teaching that more than 0% of the composition is dedicated to a contained non-specific, active substance. Thus, it would have been customary for an artisan of ordinary skill, to adjust the amount and type of active agent present in the composition, particularly in view of the varying degrees of coating hydrophilicity as practiced by Dellacherie et al. and Illum, in order to achieve the desired medicated composition. Thus, absent some demonstration of unexpected results from the claimed parameters, optimization of any of these parameters would have been obvious at the time of Applicants' invention.

All claims have been rejected; no claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/
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